The "Golden Hours" of Management in Acute Pancreatitis

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In the past decade, a significant amount of active and enthusiastic research has changed the way we treat acute pancreatitis (AP) within the first 24 hours of presentation. We highlight the importance of rapid initiation of treatment to help prevent the considerable morbidity and mortality that can occur when interventions are delayed. We review recent data that validate simple and accurate tools for prognostication of AP to replace the older, more tedious methods that relied on numerous factors and required up to 48 hours to complete. Additionally, we aim to provide evidence-based guidelines and end points for fluid resuscitation. Finally, we hope to bring clarification to two previously controversial topics in AP treatment: the use of prophylactic antibiotics and early endoscopic retrograde cholangiopancreatography.

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Introduction

Acute pancreatitis (AP) is responsible for approximately 210,000 hospital admissions per year in the United States (1), and 5% of all patients with AP die (2). Despite extensive morbidity and mortality, no targeted pharmacologic treatment exists to effectively alter the disease course. However, in the past decade, several interventions have been identified as critical in the first 24 hours to minimize morbidity and maximize survival. Comparable to the narrow diagnostic and therapeutic window in both acute cardiac and cerebral ischemia, prompt recognition and management of AP during these "golden hours" is essential to improving patient outcomes. This review highlights the importance of accurate disease prognostication and fluid resuscitation, and also clarifies issues surrounding the use of prophylactic antibiotics and early biliary intervention in patients presenting with AP.

Prognostication

Although the majority of cases of AP are categorized as mild, it is necessary to promptly identify those patients who are at risk of severe morbidity or death. Assessment of severity has been an area of intense investigation, with multiple scoring systems proposed. Until recently, no scoring system has been able to balance accuracy with simplicity. However, the Bedside Index for Severity of Acute Pancreatitis (BISAP) score was developed as a simple tool to assess risk of in-hospital mortality in AP and, to date, is the most facile tool available for predicting severity. The BISAP score is used to guide early management of AP, because of the recognition that earlier and more aggressive interventions are likely to prevent adverse outcomes, particularly in severe cases. The score is calculated with the use of five variables available in the first 24 hours: blood urea nitrogen (BUN) greater than 25 mg/dl, impaired mental status (Glasgow Coma Score less than 15), presence of the systemic inflammatory response syndrome, age greater than 60 years, and pleural effusion detected on imaging (3). It was initially validated to predict mortality on the basis of retrospective data from 18,256 cases of AP from 177 centers in 2004–2005, and was further validated prospectively on the basis of data from 397 consecutive cases in 2005–2007 (3,4). Each positive variable adds one point to the total score, and scores of 3, 4, and 5 correspond to a hospital mortality of 5.3, 12.7, and 22.5%, respectively. Additionally, the BISAP score can predict persistent organ failure (organ failure present >48 hours) (4), which is a strong independent risk factor for mortality (2).

The Harmless Acute Pancreatitis Score (HAPS) is another simple scoring system, which includes three factors that can be measured within 30 minutes of admission: absence of rebound tenderness and/or guarding, normal hematocrit, and normal serum creatinine (5). The study concluded that the HAPS predicted a nonsevere disease course with 96–97% specificity and 98% positive predictive value (5,6). However, it is unclear from the published data what the hospital interventions were in these cases. For example, if patients were treated optimally for AP with

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aggressive fluid resuscitation, pain control, and early enteral nutrition, then a severe course may have been averted in those who may have had a normal HAPS on admission but would have progressed to severe AP without those interventions.

A prospective trial comparing the BISAP scoring system with other previously proposed systems such as APACHE II and Ranson's criteria found that the BISAP score performed similarly for predicting severity, pancreatic necrosis, and mortality (7). However, both the BISAP score and the HAPS have the advantage of simplicity and timeliness when compared with these other prognostication systems. Ranson's criteria scoring cannot be completed earlier than 48 hours into the hospitalization (8). The APACHE II score was validated on critically ill patients, and calculation requires arterial blood gas, which is not routinely obtained in the emergency department, and knowledge of the patient's past medical history, which may not be attainable in the acute setting (9). The CT severity index (10) relies on contrast-enhanced computed tomography, which is generally not necessary upon presentation in most cases of AP and in fact may not be possible in the setting of renal dysfunction or hypovolemia.

These scoring systems are most useful for triage of patients without obviously severe or mild disease. Even without the use of one of the scoring systems named herein, the clinician can often judge the severity of disease on the basis of individual laboratory and physical examination findings. For example, the presence of systemic inflammatory response syndrome suggests a widespread inflammatory response that predisposes to multiple organ failure and increased disease severity (2). Additionally, laboratory markers of hemoconcentration and organ failure seem to predict severity in AP as well as more complex markers. The prognostic ability of measurements of BUN and hematocrit stems from the ability to mirror intravascular volume depletion, a critical risk factor for death in AP. In a recent validation study using three large databases including 1,043 patients with acute AP in three centers, a BUN level of 20 mg/dl or higher was associated with an odds ratio of 4.6 (95% confidence interval, 2.5–8.3) for mortality. Any rise in BUN level at 24 hours was associated with an odds ratio of 4.3 (95% confidence interval, 2.3–7.9) for death (11). Elevated hematocrit upon admission or failure of the hematocrit to decrease in the first 24–48 hours of treatment is additionally helpful in predicting a more severe disease course (12–14). In another study aimed at identification of laboratory tests to predict pancreatic necrosis, an increase in serum creatinine at 48 hours yielded a positive predictive value of 93% for the development of necrosis (14).

Ultimately the treating physician must cautiously consider all available information, taking into account patient age, laboratory and physical examination data, and comorbid conditions, including obesity. These recent simplified scoring systems, when compared with those used historically, are simple, accurate, and timely. They should enable practitioners to more rapidly triage appropriate patients to a tertiary-care center or to the intensive care unit (ICU), and allow for more informed discussions with patients and their families about prognosis at the time of hospital presentation.

Fluid resuscitation

AP initially causes the release of cytokines and other proinflammatory mediators, leading to vasodilatation, intravascular volume depletion, and end-organ hypoperfusion. Long undervalued as a life-saving intervention early in the disease course, aggressive fluid resuscitation is a cornerstone in the treatment of AP during the first 24 hours. Under-resuscitation is associated with increased morbidity (including the development of systemic inflammatory response syndrome, necrotizing pancreatitis, and organ failure) and mortality (2,15,16). Recent studies have demonstrated the critical importance of maintaining perfusion of the microcirculation of the pancreas and intestine to prevent intestinal ischemia and subsequent bacterial translocation and secondary pancreatic infection (2).

In adult patients, we almost universally begin infusion with rates of between 250 and 300 ml/h, or enough to produce at least 0.5 ml/kg/h of urine output (17). This follows a 1,000- to 2,000-ml fluid bolus given while the patient is still in the emergency room. The initial rate should be adjusted on the basis of patient age, weight, physical exam findings, and comorbid conditions such as pulmonary edema or renal failure. Hemoconcentration and elevation of BUN both reflect the amount of intravascular depletion and can be used, in addition to measurement of urine output and monitoring for the development of pulmonary edema, to guide the rate of fluid resuscitation. Since intravascular volume repletion is vital to re-establishing or maintaining the microcirculation of the pancreas, these measures should be taken into account upon admission to assist with gauging severity and again at intervals such as every 12 hours after admission (2,18). In our opinion, non-critically ill patients likely do not require placement of a Foley catheter as long as accurate intake and output can be closely monitored and recorded.

In patients with underlying cardiac or renal disease or in those of advanced age, caution should be used in administering aggressive intravenous (i.v.) fluids. These patients should be monitored closely for fluid overload via physical examination (particularly development of hypoxia, elevation of jugular venous pulsations, development of S3 on cardiac auscultation, or rales on pulmonary auscultation). In these cases, measurement of central venous pressure may be helpful. While the type of i.v. fluids has long been a source of debate, recent randomized controlled data suggest that lactated Ringer's solution may be superior to normal saline in preventing systemic inflammatory response syndrome (19).

Two studies have concluded that aggressive i.v. fluid resuscitation may be harmful; however, we believe that this conclusion is limited by the research design of these investigations. Both studies included only patients with severe AP upon admission. The first, a retrospective evaluation of 99 patients, found that patients receiving 4 liters or more in the first 24 hours developed more respiratory complications and were more likely to require ICU-level care than those who received less than 4 liters (20). It is not clear from the data precisely what the pulmonary complications were or the reasons for ICU-level care, although it is stated that pulmonary edema was not noted in any patient. More

Table 1. Summary of recommendations for the management of acute pancreatitis in the first 24 hours

Intervention	Recommendation
Prognostication of severity	Use the BISAP or HAPS score, BUN, or hematocrit
Aggressive fluid resuscitation	At least 250–300 cc/h of i.v. fluids
	Consider using lactated Ringer's solution
	Titrate level based on urine output or change in BUN and hematocrit
Prophylactic antibiotics	*No indication* for prophylactic antibiotics
Early ERCP in biliary pancreatitis	ERCP only if cholangitis or worsening cholestasis with declining clinical course

BISAP, Bedside Index for Severity of Acute Pancreatitis; BUN, blood urea nitrogen; ERCP, endoscopic retrograde cholangiopancreatography; HAPS, Harmless Acute Pancreatitis Score; i.v., intravenous.

information about these details is required before the conclusion can be drawn that the more aggressive fluid regimen led to poorer outcomes for the patients.

The second study, a randomized trial of 115 patients in China, concluded that in patients with severe AP, rapid hemodilution is associated with increased sepsis and mortality (21). However, the study was performed to target a hematocrit lower than 35% in the rapid hemodilution group and 35% or higher in the slow hemodilution group over the first 72 hours. In contrast to this approach, we recommend that fluid administration be adjusted not to a particular hematocrit level, but rather to target adequate urine output; stabilization of blood pressure and heart rate; normalization of central venous pressure; and a modest decrease in hematocrit. Additionally in this study, fluids were administered over 72 hours, with most of the fluid provided during the second 24-hour period. As has been shown in our prior research, the best outcomes are obtained when more than one-third of the 72-hour fluid total is given in the first 24 hours (15,16).

The importance of aggressive i.v. fluid resuscitation during the first 24 hours after admission for AP cannot be overstated. This intervention, although often overlooked, is a simple therapy that can dramatically improve patient outcomes.

Prophylactic antibiotics

The use of prophylactic antibiotics given at the time of detection of pancreatic necrosis in severe AP has been an area of considerable debate. A meta-analysis published in 2001 of several randomized controlled trials comparing antibiotic prophylaxis with no prophylaxis in cases of necrotizing pancreatitis showed no reduction in local pancreatic infections but significantly reduced rates of sepsis and mortality in those treated with antibiotics (21.1% and 12.3% reductions, respectively) (22). However, this meta-analysis included only three randomized controlled trials and a total of only 160 patients. In 2008, an updated meta-analysis of randomized controlled trials explored whether prophylactic antibiotics reduced infected pancreatic necrosis and mortality in necrotizing AP (23). The meta-analysis included seven trials (including the three trials in the 2001 meta-analysis) and 467 patients and found that antibiotics did not reduce the incidence of infected pancreatic necrosis ($P = 0.32$) or mortality ($P = 0.17$). A 2010 Cochrane review of the same seven trials analyzed in 2008 again found no significant difference in mortality, despite a significantly lower rate of pancreatic infection in those treated with imipenem (24).

The most recent meta-analysis, published in 2011, reviewed 14 trials with a total of 841 patients and included all of the trials included in the prior three meta-analyses, and no difference in rates of mortality or infection was detected (25). As a result of these findings, as well as the fact that prolonged prophylactic antibiotics are associated with the development of intra-abdominal fungal infections (26), prophylactic antibiotics are not recommended for use as a prophylactic therapy in AP and should not be given in the first 24 hours to prevent infection.

Acute biliary pancreatitis

Endoscopic retrograde cholangiopancreatography (ERCP) was thought to be the mainstay of early management of acute biliary pancreatitis on the basis of the hypothesis that early relief of biliary obstruction would halt the local and systemic inflammatory effects of pancreatitis as well as the progression of pancreatic necrosis. In 2007, a randomized single-center trial of 102 patients with acute biliary pancreatitis without cholangitis randomized to either early (within 72 hours) ERCP followed by endoscopic papillotomy or early conservative management found no difference between the two groups in changes in organ failure score, local complications, overall morbidity, or mortality (27). Subsequently, a prospective multicenter study comparing early ERCP with conservative management in 153 patients with predicted severe acute biliary pancreatitis without cholangitis was performed, further subdividing the group into those with cholestasis and those without cholestasis (defined as bilirubin >2.3 mg/dl and/or dilated common bile duct). The study found fewer complications in the ERCP group with cholestasis after ERCP, although there was no difference in mortality after early ERCP in either of the groups (28). A Cochrane review published in 2004 reviewed three trials with 511 patients and found significantly lower complications in patients with predicted severe acute biliary pancreatitis who underwent ERCP with or without endoscopic sphincterotomy. There was no significant difference in complications in patients with predicted mild disease, and there was no difference in mortality in either the predicted mild or the predicted severe group. Patients with cholangitis were included in the studies reviewed; however, the study authors attempted to control for confounding related to cholangitis (29). Petrov *et al.* performed a meta-analysis of five studies and found no difference in local complications (30).

On the basis of these studies, we believe ERCP should not be routinely performed in patients with biliary pancreatitis, including those with choledocholithiasis, within the first 24 hours. The only indications for ERCP within the first day are (i) AP complicated by ascending cholangitis or (ii) the development of a worsening clinical course in the context of increasing liver tests. As ERCP is a risk factor for pancreatitis, careful selection of appropriate candidates is extremely important, especially early in the course of disease. In patients with choledocholithiasis without ascending cholangitis or a deteriorating clinical course, ERCP should not be performed, and stone removal should occur only after clinical resolution of AP.

It is prudent to request involvement of a surgical team early in the course of acute biliary pancreatitis, because of the benefits of performing cholecystectomy prior to hospital discharge in order to prevent recurrence of pancreatitis and of other biliary events (31–34). Approximately 20–50% of patients will have recurrence of AP within 6–8 weeks without intervention such as cholecystectomy (31,35). In those who are deemed not to be surgical candidates, endoscopic sphincterotomy is an acceptable alternative (31,36).

It has been common practice to wait to perform surgery before hospital discharge but after the resolution of abdominal pain and normalization of laboratory studies. A more aggressive early approach may also be beneficial in patients with mild disease. In a recent randomized controlled trial of 50 consecutive patients with gallstone pancreatitis and Ranson score ≤3, laparoscopic cholecystectomy within 48 hours of admission resulted in shorter hospitalizations (mean length of stay, 3.5 vs. 5.8 days, $P = 0.0016$) and no difference in technical difficulty or perioperative complications (37).

Conclusion

In summary, the first 24 hours of care of the patient with AP is crucial to reducing the morbidity and mortality associated with this disease process (**Table 1**). During these "golden hours," initial assessment using a severity scoring system such as the BISAP or HAPS, as well as markers of hemoconcentration such as BUN and hematocrit, can guide triage and early management. Adequate early fluid resuscitation is essential to decrease inflammation and maintain organ perfusion. We recommend using lactated Ringer's solution and ongoing assessment of urine output and markers of hemoconcentration. Prophylactic antibiotics should not be routinely used, even in cases of pancreatic necrosis, unless infection is suspected on the basis of laboratory, culture, or imaging data. Early ERCP is unlikely to reduce mortality or local complications associated with AP unless the patient has concomitant ascending cholangitis or clinical deterioration in the setting of worsening cholestasis. As patients enter the second 48 hours of their hospitalization, issues such as the initiation of enteral feeding and early cholecystectomy for uncomplicated biliary pancreatitis will need to be addressed to help prevent persistent organ failure, prolonged hospitalization, readmission, or death.

CONFLICT OF INTEREST

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